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# Review of Published Studies of Orally Administered Asbestos

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**There has been great public concern about the adverse health effects resulting from the presence of asbestos fibers in municipal drinking water supplies. This article reviews and summarizes the experimental findings of 11 published papers that have evaluated the carcinogenic potential of asbestos following its ingestion. The long-term, high-level ingestion of various types of asbestos fibers in more than one animal species failed to produce any definite, reproducible, organ-specific carcinogenic effect.**

## Introduction

Prolonged industrial human exposure to asbestos has been associated with an increase in the incidence of certain forms of cancer. The relationship between inhaled asbestos and mesotheliomas of the pleura and peritoneum or pulmonary carcinoma is particularly strong; other cancers have also been implicated from inhaled asbestos (*1–3*). In order to explain why cancer may occur at remote sites following the inhalation of asbestos, it has been suggested that the asbestos fibers that are cleared from the lungs are swallowed and subsequently migrate through the gastrointestinal wall to the peritoneum where cancer may be initiated.

Originally the question of pathogenicity from asbestos exposure had relevance only to people occupationally exposed, but the discovery of amphibole fibers in municipal water supplies (*4*) indicated that asbestos was more widely dispersed through the environment than once believed. Asbestos from natural sources, as well as from mining activities, has been shown to contaminate bodies of water that are used as sources of drinking water. Asbestos fibers have been detected in commercial beverages, possibly resulting from the use of asbestos filters. The extensive use of asbestos cement pipe in municipal water systems has concerned officials of the U.S. Environmental Protection Agency. This paper summarizes the various published asbestos ingestion studies that have attempted to answer the question of whether or not ingested asbestos is a health hazard. Other relevant topics such as gastrointestinal penetration by asbestos, the presence of asbestos in municipal drinking water supplies, and epidemiologic studies will be presented in subsequent papers of this workshop. The details of all but one of the cited experimental studies are summarized in Table 1.

## Results of Published Studies

An abstract by Bonser and Clayson (*5*) initially reported experimental findings from an ingestion study. Asbestos was administered to Sprague-Dawley rats in their feed at a level of 0.15%. No malignant tumors were observed in the exposed animals, which may have been due to the low level of asbestos administered. The high mortality of the rats due to pulmonary infection seriously compromised the study.

Webster reported the only study conducted with primates (*6*). Because of lack of experimental detail, the findings of this article were omitted from Table 1. An unreported number of baboons were exposed to "heavy" concentrations of asbestos in food and drinking water for up to 5 yr. There was no evidence of any peritoneal or gastrointestinal tumors. The 5-yr exposure time appears too short for the carcinogenesis process to occur if the time element of the baboon's reaction to asbestos is similar to that of a human.

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**Table 1. Summary of asbestos ingestion studies.**

| Study | Species | Test material | Dose | Exposure time | Study duration | Number of animals, Initial/ Examined | Malignant tumors | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Number | Location | Type[a] |
| Bonser (5) | Rat | Crocidolite | 0.15% in diet *ad libitum* | To 78 wk | To 78 wk | 40/12 | 0 | | |
| | | Control | 0 | 0 | To 86 wk | 65/25 | 1 | Liver | S |
| Gross (7) | Rat | Chrysotile | 5% in diet *ad libitum* | 21 mo. | 21 mo. | 10/10 | 0 | | |
| | | Control | 0 | 0 | 21 mo. | 5/5 | 0 | | |
| | | Chrysotile | 10 mg/wk | 16 wk | To 1.5 yr | 31/31 | 2 | Breast | C |
| | | Crocidolite | 5 mg/wk | 16 wk | To 1.5 yr | 33/33 | 0 | | |
| | | Crocidolite | 10 mg/wk | 16 wk | To 1.5 yr | 34/34 | 1 | Node | L |
| | | Control | 0 | 0 | To 1.5 yr | 24/24 | 5 | 3 Breast<br>Thigh<br>Node | C<br>S<br>L |
| | | Crocidolite (2 sources) | 10 mg/wk | 18 wk | To 1.5 yr | 63/63 | 0 | | |
| | | Control | 0 | 0 | To 1.5 yr | 24/24 | 0 | | |
| Gibel (8) | Rat | Chrysotile | 20 mg/day | Life | 441[b] | 50/42 | 12 | Lung<br>4 Kidney<br>3 Node<br>4 Liver | C<br>C<br>L<br>C |
| | | Talc | 20 mg/day | Life | 649[b] | 50/45 | 3 | Liver | C |
| | | Control | 0 | 0 | 702[b] | 50/49 | 2 | Liver | C |
| Cunningham (9) | Rat | Chrysotile | 1% in diet *ad libitum* | To 24 mo. | To 24 mo. | 10/7 | 6 | Brain<br>Pituitary<br>Node<br>2 Kidney<br>Peritoneum | S<br>C<br>L<br>C<br>S |
| | | Control | 0 | 0 | To 24 mo. | 10/8 | 1 | Peritoneum | S |
| | | Chrysotile | 1% in diet *ad libitum* | To 24 mo. | To 30 mo. | 40/36 | 11 | 2 Thyroid<br>Thyroid<br>Liver<br>Chemodectoma jugular body<br>Colon<br>Ileum<br>Adrenal<br>2 Node<br>Bone | C<br>S<br>C<br><br>C<br>S<br>C<br>L<br>S |
| | | Control | 0 | 0 | To 30 mo. | 40/32 | 11 | Thyroid<br>Liver<br>2 Adrenal<br>Kidney<br>Node<br>5 Fat | C<br>C<br>C<br>C<br>L<br>S |

**Table 1. Summary of asbestos ingestion studies (continued).**

| Study | Species | Test material | Dose | Exposure time | Study duration | Number of animals, Initial/ Examined | *Malignant tumors* Number | Location | Type[a] |
|---|---|---|---|---|---|---|---|---|---|
| Wagner (*10*) | Rat | Chrysotile | 100 mg/day | 101 days/ 5 mo. | 619[b] | 32/32 | 3 | Node<br>Stomach<br>Uterus | L<br>S<br>S |
| | | Talc | 100 mg/day | 101 days/ 5 mo. | 614[b] | 32/32 | 3 | 2 Uterus<br>Stomach | S<br>S |
| | | Control | 0 | 0 | 641[b] | 16/16 | 0 | | |
| Smith (*11*) | Hamster | Amosite | 0.5 mg/L *ad libitum* | To 23 mo. | To 23 mo. | 60/60 | 1 | Lung | C |
| | | Amosite | 5 mg/L *ad libitum* | To 23 mo. | To 23 mo. | 60/60 | 3 | 2 Stomach<br>Peritoneal mesothelioma | C |
| | | Amosite | 50 mg/L *ad libitum* | To 23 mo. | To 23 mo. | 60/60 | 0 | | |
| | | Taconite tailings | 0.5 mg/L *ad libitum* | To 23 mo. | To 23 mo. | 60/60 | 1 | Uterus | S |
| | | Taconite tailings | 5 mg/L *ad libitum* | To 23 mo. | To 23 mo. | 60/60 | 0 | | |
| | | Taconite tailings | 50 mg/L *ad libitum* | To 23 mo. | To 23 mo. | 60/60 | 0 | | |
| | | Control | 0 | 0 | To 23 mo. | 120/120 | 1 | Node | L |
| Donham (*12*) | Rat | Chrysotile | 10% in diet *ad libitum* | To 32 mo. | To 32 mo. | 240/189 | 4 | 3 Colon<br>Abdominal mesothelioma | C |
| | | Cellulose fiber | 10% in diet *ad libitum* | To 32 mo. | To 32 mo. | 242/197 | 2 | Colon | C |
| | | Control | 0 | 0 | To 32 mo. | 121/115 | 3 | Colon | C |
| Ward (*13*) | Rat | Azoxymethane[c] | 7.4 mg/kg wk | 10 wk | 34 wk | 21/21 | 12 | 5 Ileum<br>7 Colon | C<br>C |
| | | Azoxymethane plus amosite | 7.4 mg/kg wk<br>10 mg 3/wk | 10 wk | 34 wk | 21/18 | 10 | 3 Ileum<br>7 Colon | C<br>C |
| | | Azoxymethane plus chrysotile | 7.4 mg/kg wk<br>10 mg 3/wk | 10 wk | 34 wk | 21/21 | 10 | 4 Ileum<br>6 Colon | C<br>C |

**Table 1. Summary of asbestos ingestion studies (continued).**

| Study | Species | Test material | Dose | Exposure time | Study duration | Number of animals, Initial/ Examined | Malignant tumors | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Number | Location | Type[a] |
| Ward (*13*) | Rat | Amosite | 10 mg 3/wk | 10 wk | 34 wk | 21/21 | 0 | | |
| | | Chrysotile | 10 mg 3/wk | 10 wk | 34 wk | 21/21 | 0 | | |
| | | Saline | 1.0 mL 3/wk (gavage) | 10 wk | 34 wk | 21/21 | 0 | | |
| | | Untreated | — | 0 | 34 wk | 21/21 | 0 | | |
| | | Azoxymethane | 7.4 mg/kg wk | 10 wk | To 95 wk | 50/48 | 39 | 12 Ileum<br>27 Colon | C<br>C |
| | | Azoxymethane plus amosite | 7.4 mg/kg wk<br>10 mg 3/wk | 10 wk | To 95 wk | 50/48 | 44 | 15 Ileum<br>29 Colon | C<br>C |
| | | Saline plus amosite | 1/wk (SC)<br>10 mg 3/wk | 10 wk | To 95 wk | 50/49 | 17 | Ileum<br>16 Colon | C<br>C |
| Hiding (*14*) | Rat | Filtered Duluth tapwater | 1 mfl[d]<br>*ad libitum* | 690[b] | 690[b] | 28/27 | 3 | Lung<br>Ovary<br>Forestomach | C<br>C<br>C |
| | | Unfiltered Duluth tapwater | 100 mfl<br>*ad libitum* | 960[b] | 960[b] | 30/28 | 4 | Salivary gland<br>Skin<br>Uterus<br>Mediastinum | C<br>C<br>S<br>L |
| | | Lake Superior water sediment | 5,000 mfl<br>*ad libitum* | 840[b] | 840[b] | 22/22 | 3 | Lung<br>Skin<br>Uterus | C<br>C<br>S |
| | | Taconite tailings | 100,000 mfl<br>*ad libitum* | 870[b] | 870[b] | 30/30 | 3 | Neck<br>Chest wall<br>Mediastinum | S<br>S<br>L |
| | | Chrysotile/ amosite | 20 mg/day | 870[b] | 870[b] | 30/30 | 6 | Breast<br>2 fibrous histiocytoma<br>Skin<br>Mediastinum<br>Pleural mesothelioma | C<br><br>C<br>L |
| | | Amosite | 300 mg/day | 750[b] | 750[b] | 20/20 | 1 | Leukemia | |
| | | Diatomaceous earth | 20 mg/day | 840[b] | 840[b] | 30/30 | 5 | Salivary gland<br>2 Uterus<br>Skin<br>Peritoneal mesothelioma | C<br>S<br>C |

**Table 1. Summary of asbestos ingestion studies (continued).**

| Study | Species | Test material | Dose | Exposure time | Study duration | Number of animals, Initial/ Examined | Malignant tumors | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Number | Location | Type[a] |
| Bolton (*15*) | Rat | Amosite | 250 mg/wk | 25 mo. | Life | 24/24 | 1 | Stomach | S |
| | | Crocidolite | 250 mg/wk | 25 mo. | Life | 22/22 | 1 | Adrenal | C |
| | | Chrysotile | 250 mg/wk | 25 mo. | Life | 22/22 | 5 | Fat | S |
| | | | | | | | | Pleural histiocytoma, | |
| | | | | | | | | 2 Adrenal | C |
| | | | | | | | | Plasma cell tumor | |
| | | Margarine control | 0 | 0 | Life | 24/24 | 4 | 2 Adrenal | C |
| | | | | | | | | Bladder | C |
| | | | | | | | | Peritoneum | S |
| | | Control | 0 | 0 | Life | 23/23 | 2 | Fat | |
| | | | | | | | | Lymphoma | S |

[a]Type C = carcinoma; S = sarcoma; L = lymphoma.
[b]Mean survival time in days.
[c]Azoxymethane given subcutaneously; saline administered by oral gavage or subcutaneously.
[d]mfl = million amphibole fibers/L

The results of a series of feeding experiments with different sources of chrysotile and crocidolite were reported by Gross et al. (*7*). This paper incorporated data from unpublished results of various studies conducted by three laboratories. Animals fed asbestos by gavage in butter or margarine for up to 21 months failed to provide evidence of a carcinogenic effect. The experiments were flawed for the following reasons: the number of rats in the experimental groups was small, the doses of asbestos were limited, significant information on experimental protocol was missing, and systematic histologic examination was not performed on a significant number of rats.

A study by Gibel et al. (*8*) was undertaken to feed asbestos filter material to rats because of the concern of the possible adverse health effects of erosion of asbestos from the filters used to purify commercial beverages. The filter material was composed of sulfated cellulose, a condensation resin and chrysotile asbestos (53%). The authors did not provide any information regarding the size and shape of the asbestos fibers that were incorporated into the filter material. Although 12 malignant tumors were noted in the asbestos-exposed group of rats and the mean survival time was decreased in the asbestos-treated group, the authors stated that no conclusions could be made from their test results regarding the pathogenesis of the tumors caused by the oral intake of asbestos material. The relationship of this study to asbestos carcinogenicity was also confounded by the presence of several substances in the filter material, which were not clearly identified.

Cunningham and co-workers (*9*) conducted two limited feeding studies with male Wistar rats. Chrysotile asbestos (1% with 5% corn oil) was added to rat chow and fed to the animals for 24 months or 30 months. In the first study, 10 rats were exposed to asbestos. Six of the seven rats autopsied were found to have tumors, while only one malignancy was observed in the control animals. In the larger study of 80 animals, equal numbers of malignant tumors were noted in the exposed and the control groups. The authors stated that trace amounts of asbestos can penetrate the walls of the gastrointestinal tract, but evidence that asbestos causes cancer by the oral route of administration was inconclusive.

Wagner et al. (*10*) fed 32 Wistar rats 100 mg/day of chrysotile or talc in malted milk for 101 days over a 5-month period. A slight decrease in survival time was observed in the two experimental groups. One gastric leiomyosarcoma was detected in each exposure group. Interpretation of the results of this experiment is difficult because of the small number of animals included in the study.

A study in Smith's laboratory (*11*), which was the first study to utilize a large number of ani-

mals, was designed to more closely simulate an environmental exposure to asbestos. Hamsters were exposed to either amosite fibers or taconite tailings at three different dose levels in drinking water. The control animals received Lake Superior water that had been filtered by either a 0.45-μm or 0.1-μm filter. A small number of malignant tumors was detected in the exposed groups, but these tumors were not specifically attributed to asbestos because no cancers were detected in the high dose groups. The particle size of the different fiber types was well characterized by the investigators.

Another large lifetime animal study by Donham et al. (*12*) was initiated to induce and to characterize colon lesions in F344 rats by feeding them high levels of asbestos (10% of feed). Because of the high level of asbestos in the feed, a nonnutritive cellulose fiber control group was included. In this study only the colon and rectum were examined microscopically. Although differences in the number of colon tumors were not statistically significant between the asbestos-fed animals and control groups, the researchers presented the following observations, which suggest that ingested asbestos is not inert in the colon: evidence of increased probability of asbestos-fed rats to develop colon lesions generally, evidence for unique mesothelioma in rats fed asbestos, evidence for a colonic cell regulator defect, and evidence for asbestos fiber penetration of colon mucosa.

Two experiments were designed by Ward et al. (*13*) to determine the promoter potential of oral exposure to asbestos. Could asbestos modify the response to azoxymethane, a known intestinal carcinogen? Rats were exposed to azoxymethane and/or asbestos for 10 weeks and were sacrificed 34 weeks later or observed throughout their lifespan. In the first experiment, intestinal carcinomas were detected only in the groups of animals receiving azoxymethane alone or in combination with asbestos. In the second experiment of longer duration, the incidence of intestinal tumors was only slightly greater in the amosite plus azoxymethane group as compared with the azoxymethane group. Furthermore, the authors concluded that amosite alone caused a relatively high rate of intestinal neoplasia. However, there were no control animals included in the second experiment, which compromises the findings. The researchers reported a 14% incidence of Zymbal gland tumors in the rats exposed only to amosite. The historical rate of Zymbal gland tumors in the National Cancer Institute Bioassay Program is 0.34%, indicating that it is a relatively rare tumor. Since a single dose of azoxymethane has been shown to induce both Zymbal gland tumors and intestinal carcinomas (*14*), an inadvertent exposure to azoxymethane might have caused the high incidence of intestinal neoplasma and Zymbal gland tumors in the amosite-exposed animals. One has reason to doubt the authors' conclusion that oral asbestos exposure in F344 rats may have increased the incidence of intestinal tumors occurring naturally.

Since amphibole fibers had been detected in Lake Superior and in the Duluth municipal water supply, a study was conducted by Hilding et al. (*15*) to investigate the potential carcinogenic effect of unfiltered Duluth tapwater, municipal water reservoir sediments, taconite plant tailings, amosite, and diatomaceous earth. Under the experimental conditions of this study, no significant increases were detected in the incidence of malignant tumors in any experimental group when compared to controls.

The final study (*16*) considered in this review examined the effects of prolonged asbestos exposure to rats. Animals were fed over 250 mg/week of amosite, crocidolite and chrysotile in margarine for periods up to 25 months. No excess of malignant tumors were found in any experimental group, and no gastrointestinal mucosal abnormalities were detected. Bolton and co-workers concluded that there were no significant adverse health effects from prolonged asbestos ingestion in healthy laboratory rats.

## Conclusions

Certain conclusions can be summarized from the various ingestion studies. The bulk of the experimental evidence indicates that the long-term, high-level ingestion exposure to various types of asbestos fibers failed to produce any definite, reproducible, organ-specific carcinogenic effect. Although comparisons between studies are confounded by different rat strains utilized, by different dose levels or exposure conditions, and by different types of asbestos employed, the vast majority of the asbestos ingestion studies were either negative or equivocal. There was apparently a carcinogenic response to amosite in one study (*13*), but the authors did not rule out that an inadvertent exposure to azoxymethane, an intestinal carcinogen, had occurred. Many of the studies suffered from an insufficient number of experimental animals and from an inadequate exposure time to asbestos. Another major drawback of many of the studies was that they were not lifetime studies.

One can question the suitability of the animal models employed in evaluating the human response to oral exposure to asbestos, since sufficient time may be lacking between exposure and the development of malignancies during the animal's lifetime. However, exposure to asbestos by other routes has induced cancer in rats. For example, Wagner et al. (*17*) reported the development of lung cancer and mesothelioma from brief to lengthy inhalation exposure to various types of asbestos, while Gross (*18*) reported asbestotic lung cancers in 25 of 72 rats that survived 16 months of exposure to chrysotile dust. Based on the carcinogenic effects of asbestos from nonoral exposure routes (*2,3*), one would expect to be able to produce a neoplastic response within the lifetime of conventional laboratory animals with massive doses of ingested asbestos such as those employed in some of the studies mentioned in this paper. These studies also cast some doubt on the hypothesis that peritoneal mesotheliomas and gastrointestinal cancers result from the ingestion of asbestos fibers cleared from the lungs following inhalation exposure.

The research described in this paper has been peer and administratively reviewed by the U.S. Environmental Protection Agency and approved for presentation and publication. Mention of trade names or commercial products does not constitute endorsement of recommendation for use.

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